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(71) Applicant: **ALTERGON S.A.**
Via Dogana Vecchia, 2
CH-6900 Lugano(CH)

(72) Inventor: **Donati-Pedemonti, Elisabetta**
Via Rimembranza 1/B
I-22100 Como(IT)
Inventor: **Lualdi, Paolo**
Via Baradello 1
I-22070 Grandate(Como)(IT)

(74) Representative: **Gervasi, Gemma et al**
NOTARBARTOLO & GERVASI Srl Viale Bianca Maria 33
I-20122 Milan(IT)

(54) Topical compositions containing diclofenac.

(57) The invention relates to pharmaceutical compositions comprising a non-steroid antiinflammatory drug, namely diclofenac hydroxyethylpyrrolidine (DIEP), suitably carried by lipid substances of amphipathic character to allow topical application, with adequate cutaneous absorption.

EP 0 372 527 A1

LIPID PHARMACEUTICAL COMPOSITIONS FOR TOPICAL USE, ABLE TO ACT AS VEHICLES FOR A WATER-SOLUBLE ANTIINFLAMMATORY ACTIVE PRINCIPLE

Prior art

Those substances which possess maximum cutaneous absorption levels are known to present amphipathic characteristics of between 4 and 15 expressed as the HLB (hydrophil-lipophil balance) value (Remington's Pharmaceutical Sciences, Easton Penna, 1975, USA) and a very low degree of ionization.

Diclofenac hydroxyethylpyrrolidine (DIEP) is soluble in water to concentrations exceeding 50% (w/v) in which it ionizes practically totally, but is only slightly soluble in polar organic solvents, and is practically insoluble in apolar organic solvents.

These physico-chemical characteristics mean that a product dissolved in a water phase cannot be satisfactorily absorbed by the cutis, as demonstrated by the insufficient antiinflammatory activity obtained when DIEP is applied in the form of medicated gels based on cellulose or acrylic derivatives, such as those of the following compositions.

Composition I:	
DIEP	1.32%
Neutralized polymerized acrylic acid	2.00%
Isopropyl alcohol	10.00%
Demineralized water to make up to	100.00%

Composition II:	
DIEP	1.32%
Glycerin	25.00%
Hydroxyethylcellulose	2.00%
Parabens	0.80%
Demineralized water to make up to	100.00%

Summary of the invention

We have now discovered new pharmaceutical compositions for topical use able to act as improved vehicles for diclofenac hydroxyethylpyrrolidine (DIEP). Said compositions comprise:
diclofenac hydroxyethylpyrrolidine (DIEP), lipid substances of amphipathic character with high cutaneous absorption, suitable surfactants, co-solvents and additives of common pharmaceutical use suitable for topical application, incorporated in a viscous hydrophilic support (gel).

Said compositions are prepared by dissolving the DIEP in the liquid substances in the presence of surfactants, co-solvents and additives, and emulsifying the obtained mixture together with the viscous hydrophilic support.

The compositions obtained have physico-chemical characteristics which indicate their suitability for cutaneous absorption and are easy to apply locally.

Detailed description of the invention

The characteristics and advantages of the pharmaceutical compositions for topical use according to the invention will be more apparent from the following detailed description.

Said compositions comprise diclofenac hydroxyethylpyrrolidine (DIEP) as active principle and, as vehicles, lipid substances of amphipathic character, surfactants, co-solvents and additives of common

pharmaceutical use, and are incorporated in a viscous hydrophilic support (gel).

Of the possible lipid substances which can be used, those pertaining to the following four groups are preferred:

1) Cetyl and stearyl esters of ethylhexanoic acid which have been made hydrophilic by surfactants, and have an HLB of between 10 and 12;

2) C_8-C_{18} mono and/or di and/or triglycerides with different polyoxyethylenated/glycolyzed aliphatic chains, and having an HLB of between 4 and 14;

3) Phospholipids of vegetable origin having an HLB of between 12 and 14;

4) Lanolin esters having an HLB of 9.

The dissolving of the DIEP in said lipid compounds is aided by adding non-ionic surfactants having an HLB of between 10 and 13, such as polyethyleneglycol stearates, cetomacrogols etc.

The co-solvents used can be glycols, ethyldiglycol or low molecular-weight polyethyleneglycols, which also perform a wetting action in the complete formulation.

The lipid solutions obtained are emulsified in a transparent hydrophilic gel consisting of suitably neutralized polymerized acrylic acid. A gel is obtained having a milky or transparent appearance, and of suitable viscosity and consistency for application to the skin.

The composition is completed by the addition of additives of common pharmaceutical use such as antimicroblals, for example nipaginics, isopropyl alcohol, perfumes etc.

In the compositions of the present invention the various components are contained in the following weight proportions: DIEP between 0.5 and 2%, lipids between 1 and 5%, surfactants between 1 and 10%, co-solvents between 3 and 12%, acrylic acid between 0.5 and 3%, and other commonly used additives between 7 and 15%, the difference to 100% being demineralized water.

When used topically, the compositions prepared in this manner are easily absorbed to carry the DIEP into the dermis where it efficiently performs its pharmacological action.

The following examples of compositions according to the present invention are given for illustrative purposes.

EXAMPLE 1	
	% by weight
DIEP	0.5- 2
acetylstearyl-2-ethylhexanoate	1 - 4
polyethyleneglycol 400 stearate	1 - 2
polyethyleneglycol 300 or propyleneglycol	5 - 10
polymerized acrylic acid	0.5- 3
triethanolamine	1 - 4
isopropanol	6 - 10
perfume	0.1 - 0.2
demineralized water to make up to	100

EXAMPLE 2	
	% by weight
DIEP	0.5- 2
cetylstearyl-2-ethylhexanoate	1 - 2
cetomacrogol stearyl alcohol	1 - 2
polyethyleneglycol 300 or propyleneglycol	5 - 10
polymerized acrylic acid	0.5- 3
triethanolamine	1 - 4
isopropanol	6 - 10
perfume	0.1- 0.2
demineralized water to make up to	100

EXAMPLE 3	
	% by weight
DIEP	0.5- 2
polyoxyethylenated C_{12}-C_{18} glycerides	1 - 4
ethyldiglycol	3 - 8
polyethyleneglycol 400 stearate	1 - 2
polymerized acrylic acid	0.5- 3
triethanolamine	1 - 4
isopropanol	6 - 10
perfume	0.1- 0.2
demineralized water to make up to	100

EXAMPLE 4	
	% by weight
DIEP	0.5- 2
polyoxyethylenated ricinoleic triglyceride	0.5- 5
polyethyleneglycol 400 stearate	1 - 2
propyleneglycol	5 - 10
polymerized acrylic acid	0.5- 3
triethanolamine	1 - 4
isopropanol	6 - 10
perfume	0.1- 0.2
demineralized water to make up to	100

EXAMPLE 5	
	% by weight
DIEP	0.5- 2
soya lecithin	2 - 5
polyethyleneglycol 400 stearate	1 - 2
glycerin	5 - 10
polymerized acrylic acid	0.5- 3
triethanolamine	1 - 4
isopropanol	6 - 10
perfume	0.1- 0.2
demineralized water to make up to	100

EXAMPLE 6	
	% by weight
DIEP	0.5- 2
isopropyl lanolate	1 - 4
glyceryl monostearate or polyethyleneglycol 400 stearate	1 - 4
propyleneglycol	6 - 12
polymerized acrylic acid	0.5- 3
triethanolamine	1 - 4
isopropanol	6 - 10
perfume	0.1- 0.2
dimineralized water to make up to	100

By way of example, the antiinflammatory activity results obtained experimentally in the rat by applying 1 gram of some of the aforesaid preparations indicated with 1-4-5 are shown hereinafter, compared with those of a hydrophilic gel containing the same concentration of DIEP (Composition I of the known art).

Preparation	DIEP concentration	Quantity applied to rat	No. of rats	Analgesic/peripheral anti-inflammatory activity (Randall-Selitto test)
1	1.32%	1 g	5	65%
4	1.32%	1 g	5	72%
5	1.32%	1 g	5	68%
Hydrophilic gel (Composition I)	1.32%	1 g	5	22%

These results clearly indicate the considerable increase in absorption of the active principle obtained with the compositions according to the present invention.

Claims

1. Pharmaceutical compositions for topical use able to act as vehicles for diclofenac hydroxyethyl-pyrrolidine (DIEP), characterised by comprising diclofenac hydroxyethylpyrrolidine (DIEP), lipid substances of amphipathic character with high cutaneous absorption, suitable surfactants, co-solvents and additives of common pharmaceutical use, said compositions being incorporated in a viscous hydrophilic support.

2. Compositions as claimed in claim 1, characterised in that said lipid substances are the cetyl and

stearyl esters of ethylhexanoic acid made hydrophilic by surfactants, and having an HLB of between 10 and 12.

3. Compositions as claimed in claim 1, characterised in that said lipid substances are C_8-C_{18} mono and/or di and/or triglycerides with different polyoxyethylenated/glycolyzed aliphatic chains, with an HLB of between 4 and 14.

4. Compositions as claimed in claim 1, characterised in that said lipid substances are phospholipids of vegetable origin with an HLB of between 12 and 14.

5. Compositions as claimed in claim 1, characterised in that said lipid substances are lanolin esters with an HLB of 9.

6. Compositions as claimed in claim 1, characterised in that said surfactants are of non-ionic type with an HLB of between 10 and 13.

7. Compositions as claimed in claim 6, characterised in that said surfactants are polyethyleneglycol stearates and cetomacrogols.

8. Compositions as claimed in claim 1, characterised in that said co-solvents are glycols, ethyldiglycol and low molecular weight polyethyleneglycols.

9. Compositions as claimed in claim 1, characterised in that said viscous hydrophilic support is neutralized polymerized acrylic acid.

10. Compositions as claimed in claim 1, characterised by comprising the various components in the following weight proportions: DIEP between 0.5 and 2%, lipids between 1 and 5%, surfactants between 1 and 10%, co-solvents between 3 and 12%, acrylic acid between 0.5 and 3%, and other commonly used additives between 7 and 15%, the difference to 100% being demineralized water.

11. A method for preparing the compositions claimed in claims 1 to 10, characterised in that the DIEP is dissolved in the lipid substances in the presence of the surfactants, co-solvents and additives, the mixture obtained then being emulsified with the viscous hydrophilic support.

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EUROPEAN SEARCH REPORT

Application Number

EP 89 12 2486

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
A	EP-A-0 271 709 (ALTERGON) * Claims 1,8-10; page 3, lines 17-26 * ---	1,8,10	A 61 K 31/195 A 61 K 47/14 A 61 K 47/24 A 61 K 47/32 A 61 K 47/00
A	CHEMICAL ABSTRACTS, vol. 105, no. 12, 22nd September 1986, page 336, abstract no. 102589c, Columbus, Ohio, US; & IL-A-62 160 (CIBA LTD) 29-09-1985 * Abstract * -----	1,8,10	

TECHNICAL FIELDS SEARCHED (Int. Cl.5)

A 61 K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	14-03-1990	SCARPONI U.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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